PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: A61K 47/48	A2	(11) International Publication Number:	WO 00/37110
		(43) International Publication Date:	29 June 2000 (29.06.2000)

(21) International Application Number: PCT/US99/27935

(22) International Filing Date: 16 December1999 (16.12.1999)

(30) Priority Data:
09/215,876 18 December1998 (18.12.1998) US

(60) Parent Application or Grant
SCHERING CORPORATION [/]; (). GLUE, Paul, W. [/]; (). ALBRECHT, Janice, K. [/]; (). HOFFMAN, Thomas, D. ; ().

Published

(54) Title: RIBAVIRIN-PEGYLATED INTERFERON ALFA INDUCTION HCV COMBINATION THERAPY

(54) Titre: TRAITEMENT DU VHC PAR INDUCTION D'INTERFERON-ALPHA PEGYLE COMBINE LA RIBAVIRINE

(57) Abstract

The use of ribavirin and interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatitis C infection, e.g., a patient having HCV genotype 1, 2 or 3, to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period of at least 20 to 30 wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa, e.g., pegylated interferon-alfa-2b sufficient to at least substantially lower, and preferably to eradicate, detectable HCV-RNA, are administered; and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to maintian no detectable HCV-RNA for at least 20-30 weeks are administered after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period is disclosed.

(57) Abrégé

L'invention concerne l'utilisation de ribavirine et d'interféron alpha pour la préparation de compositions pharmaceutiques dans le traitement d'un patient souffrant d'hépatite C chronique, notamment un patient dont le génotype du VHC est 1, 2 ou 3. Cette utilisation vise à éradiquer le taux de l'ARN du VHC détectable en mettant un oeuvre un procédé consistant à administrer une quantité efficace de ribavirne associée à une quantité efficace d'interféron alpha pégylé. Le traitement du patient souffrant d'hépatite C chronique s'effectue en deux temps : a) une première période d'au moins 20 à 30 semaines au cours de laquelle on administre une quantité thérapeutiquement efficace de ribavirine et une quantité inductive thérapeutiquement efficace d'interféron alpha pégylé, à savoir l'interféron alpha pégylé 2b en doses suffisantes pour diminuer considérablement et supprimer; dans la mesure du possible, le taux de l'ARN du VHC détectable; et b) une seconde période de traitement s'étendant sur 20 à 30 semaines au cours de laquelle on administre une quantité thérapeutiquement efficace de ribavirine et une quantité thérapeutique efficace d'interféron alpha pégylé en quantités suffisantes pour que le taux de l'ARN du VHC ne soit pas détectable pendant au moins 20 à 30 semaines après la fin de la période du premier traitement et en quantités suffisantes pour que le taux de l'ARN VHC ne soit pas détectable pendant au moins 24 semaines une fois que le second traitement est terminé.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 47/48

A2

(11) International Publication Number: WO 00/37110

(43) International Publication Date: 29 June 2000 (29.06.00)

(21) International Application Number: PCT/US99/27935

(22) International Filing Date: 16 December 1999 (16.12.99)

(30) Priority Data:
09/215,876 18 December 1998 (18.12.98) US

(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).

(72) Inventors: GLUE, Paul, W.; 13 Allens Corner Road, Flemington, NJ 08822 (US). ALBRECHT, Janice, K.; 1308 Temple Grove Court, Winter Park, FL 32789 (US).

(74) Agents: HOFFMAN, Thomas, D. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: RIBAVIRIN-PEGYLATED INTERFERON ALFA INDUCTION HCV COMBINATION THERAPY

(57) Abstract

The use of ribavirin and interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatitis C infection, e.g., a patient having HCV genotype 1, 2 or 3, to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period of at least 20 to 30 wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa, e.g., pegylated interferon-alfa-2b sufficient to at least substantially lower, and preferably to eradicate, detectable HCV-RNA, are administered; and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to maintian no detectable HCV-RNA for at least 20-30 weeks are administered after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period is disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Description

RIBAVIRIN-PEGYLATED INTERFERON ALFA INDUCTION HCV COMBINATION THERAPY

BACKGROUND OF THE INVENTION

The present invention relates to the use of ribavirin, pegylated interferon alfa and compbinations thereof for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised by administering a therapeutically effective induction amount of ribavirin and a therapeutically effective induction amount of pegylated interferon-alfa for a first treatment time period sufficient to substantially lower detectable HCV-RNA, followed by (2) administering a therapeutically effective amount of ribavirin and an therapeutically effective amount of pegylated interferon-alfa for a second treatment time period sufficient to eradicate detectable HCV-RNA at least by the end of the second treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

Chronic infection with hepatitis C virus is an insidious and slow-progressing disease having a significant impact on the quality of life. It can eventually result in cirrhosis of the liver, decompensated liver disease and/or hepatocelluar carcinoma.

International Publication No. WO98/48840 discloses use of pegylated interferon alfa to treat hepatitis C infections.

Nieforth *et al.* (Clin. Pharmacol. Ther., 1996, 59:636-646) has reported a comparison of the *in vivo* activity of Roferon®A and a polyethylene glycol-modified Roferon®A in healthy volunteers. The

results, however, suggested that the conjugates could not be administered less than twice weekly and therefore offered little therapeutic advantage over the unmodified counterpart.

Co-pending, commonly assigned U.S. Patent Application Serial No. 08/742,305 discloses methods of administering polymer-cytokine conjugates to individuals susceptible to treatment with the cytokine, but does not disclose the method of this invention.

Polyethylene glycol modification of other proteins has been reported by Fuertges et al. (Journal of Controlled Release,1990, Vol.11:139-48).

Combination therapy of interferon alfa-2b and ribavirin to treat chronic hepatitis C for 24 weeks is disclosed by Reichard et al. (Lancet 1998; 351;83-87)

T. Poynard et al. (Lancet, 1998, Vol. 352, 1426-1432) disclose that treating chronic hepatitis C patients who had not been treated with interferon or ribavirin with 3 MIU of interferon alfa-2b TIW plus 1000-1200 mg of ribavirin per day for 48 weeks resulted in a sustained virological response at 24 weeks after treatment in 43% of the patients. See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499) disclose that treating chronic hepatitis C patients who relapsed after treatment with interferon with 3 MIU of interferon alfa 2b Tim plus 100-1200 mg of ribavirin per day for 48 weeks results in higher rates of sustained virologic response than treatment with interferon alone.

There is a need to provide an improved therapy for treating chronic hepatitis C patients to produce a sustained virological response at 24 weeks after treatmen in agreater number of patients.

SUMMARY OF THE INVENTION

The present invention provides the use of ribavirin for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods:(a) a first treatment time period, wherein a therapeutically effective amount of ribavirin and an therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to sustantially lower detectable HCV-RNA serum levels, and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to eradicate detectable HCV-RNA at least 20 to 30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

The present invention also provides the use of pegylated interferon alpha for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of pegylated interferon alpha in association with an effective amount of ribavirin characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period,wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to sustantially lower detectable HCV-RNA serum levels, and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to eradicate detectable HCV-

RNA at least 20 to 30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

The present invention also provides the use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period, wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to sustantially lower detectable HCV-RNA serum levels, and by (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to eradicate detectable HCV-RNA at least 20 to 30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

The present invention also provides the use of ribavirin for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period, wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to eradicate detectable HCV-RNA, and (b) a second treatment time period of at least 20 to 30

weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to maintain no detectable HCV-RNA for at least 20-30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

The present invention also provides the use of pegylated interferon alpha for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of pegylated interferon alpha in association with an effective amount of ribavirin characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period, wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to eradicate detectable HCV-RNA, and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to maintain no detectable HCV-RNA for at least 20-30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

The present invention also provides the use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period, wherein a therapeutically effective amount of

ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to eradicate detectable HCV-RNA, and (b) a second treatment time period of at least 20 to 30 weeks a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to maintain no detectable HCV-RNA for at least 20-30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

The present invention also provides the use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (1) a first treatment time period of about at least about four weeks, wherein about 400-1200 mg per day, preferably about 800-1200 mg per day, of ribavirin and about 1.5 micrograms per kilogram of pegylated interferon-alfa-2b twice a week are administered, (2) a second treatment time period of about up to about forty-four weeks, wherein about 800-1200 mg per day of ribavirin and about 1.0 to 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week are administered.

The present invention also provides the use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (1) a first treatment time period of about at least about four up to about twelve

weeks, wherein about 400-1200 mg per day, preferably about 800-1200 mg per day, of ribavirin and about 1.5 micrograms per kilogram of pegylated interferon-alfa-2b twice a week are administered, (2) a second treatment time period of about thirty-six up to about forty-four weeks, wherein about 800-1200 mg per day of ribavirin and about 0.5 to 1.5 micrograms per kilogram once a week, preferably about 1.0 to 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week are administered.

DETAILED DESCRIPTION

The present method of treating patients having chronic hepatitis C infections comprises two treatment time periods. In the first treatment time period, a therapeutically effective induction dosing amount of ribavirin and an therapeutically effective induction dosing amount of pegylated interferon-alfa is administered for a first treatment time period sufficient to substantially lower detectable HCV-RNA serum levels, preferably by a power of 10, more preferrably by at least two powers of ten, i.e., at least 10^2, lower than the initial HCV-RNA serum level. In a preferred embodiment of the present invention, the HCV-RNA is eradicated (i.e.,lowered to less than 100 copies/mL) during the first treatment time period. In the second treatment time period, the method entails administering a therapeutically effective amount of ribavirin and an therapeutically effective amount of pegylated interferon-alfa long enough to eradicate detectable HCV-RNA at least by the end of the second treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period. In a preferred embodiment of the present invention , the HCV-RNA is eradicated (i.e., lowered to less than 100 copies/mL) during the second treatment time period and more preferably by the end of the first treatment time period; in this preferred embodiment the no detectable HCV-RNA level is maintained during the second treatment time period. The sum of

the first and second treatment time periods is about 40-50 weeks preferrably 48 weeks.

The amount of ribavirin administered in the first treatment time period is from 400 to 1600 mg per day, preferrably 600 to 1200 mg/day or about 800 to 1200 mg day and most preferably about 1000 to 1200 mg/kg a day. The amount of ribavirin administered in the second treatment time period is in the range of from about 800 to 1200 mg per day, preferably from about 1000 to 1200 mg per day.

The following preferred embodiments for administering pegylated interferon alfa are presented.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period is in the range of 0.5 to 1.5 micrograms per kilogram twice a week (BIW) for at least four up to twelve weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period is in the range of 0.5 to 1.5 micrograms per kilogram once a week (QW) for thirty-six up to to forty-four weeks.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period is in the range of 0.5 to 1.5 micrograms per kilogram twice a week (BIW) for twelve weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period is in the range of 0.5 to 1.5 micrograms per kilogram once a week (QW) for thirty-six weeks.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period of five weeks is in the

range of 0.5 to 1.5 micrograms per kilogram BIW (preferably 1.5microgram per kilograms BIW) for one week, followed by 0.5 to 1.0 micrograms per kilogram BIW (preferably 1.0 micrograms per kilogram BIW) for four weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period of forty-three weeks is in the range of 0.5 to 1.5 micrograms per kilogram once a week, prefrably 0.5 to 1.0 micrograms per kilogram once a week.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period is in the range of 1.5 microgram per kilogram BIW for four weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period is in the range of 0.5 micrograms per kilogram once a week for to forty-four weeks.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period of five weeks is in the range of 1.5 micrograms per kilogram BIW for one week, followed by 1.0 micrograms per kilogram BIW for four weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period of thirty-six to forty-four weeks is in the range of 0.5 to 1.0 micrograms per kilogram once a week.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period is 1.5 micrograms per kilogram BIW for twelve weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period is in the range 1.0 micrograms per kilogram once a week for thirty-six weeks.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the induction dosing amount of pegylated interferon alfa-2a administered in first treatment time period is in the range of 20 to 250 micrograms BIW, preferably 90 to 180 micrograms BIW, for at least four weeks, and the amount of pegylated interferon alfa-2a administered in the second treatment time period is in the range of 20 to 250 micrograms once a week(QW), preferably 90 to 180 micrograms QW, for up to forty-four weeks.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the induction dosing amount of pegylated interferon alfa-2a administered in first treatment time period is in the range of 20 to 250 micrograms BIW, preferably 90 to 180 micrograms BIW, for four to twelve weeks, and the amount of pegylated interferon alfa-2a administered in the second treatment time period is in the range of 20 to 250 micrograms once a week, preferably 90 to 180 micrograms QW, for thirty-six to forty-four weeks.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the induction dosing amount of pegylated interferon alfa-2a administered in first treatment time period is in the range of 20 to 250 micrograms BIW for one week, preferably 90 to 180 micrograms BIW for one week, followed by 20 to 200 micrograms BIW for four weeks, preferably 90 to 180 micrograms BIW for four weeks and the amount of pegylated interferon alfa-2a administered in the second treatment time period is in the range of 20 to 250 micrograms once a week(QW), preferably 90 to 180 micrograms QW for forty-three weeks.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, in first treatment time period, the induction dosing amount of pegylated interferon alfa-2a administered is in the range of 20 to 250 micrograms BIW, preferably 90 to 180 micrograms BIW, for twelve weeks, and the amount of pegylated interferon alfa-2a administered in the

second treatment time period is in the range of 20 to 250 micrograms per week on a weekly basis(QW), preferably 90 to 180 micrograms QW, for thirty-six weeks.

The term "pegylated interferon alfa" as used herein means polyethylene glycol modified conjugates of interferon alfa, preferably interferon alfa-2a and -2b. The preferred polyethylene-glycol-interferon alfa -2b conjugate is PEG_{12000}-interferon alfa 2b. The phrases "12,000 molecular weight polyethylene glycol conjugated interferon alpha" and "PEG_{12000}-IFN alfa" as used herein mean conjugates such as are prepared acording to the methods of International Application No. WO 95/13090 and containing urethane linkages between the interferon alfa-2a or -2b amino groups and polyethylene glycol having an average molecular weight of 12000.

The preferred PEG_{12000}-interfferon alfa-2b is prepared by attaching a PEG polymer to the epsilon amino group of a lysine residue in the IFN alfa-2b molecule. A single PEG_{12000} molecule is conjugated to free amino groups on an IFN alfa-2b molecule via a urethane linkage. This conjugate is characterized by the molecular weight of PEG_{12000} attached. The PEG12000-IFN alfa-2b conjugate is formulated as a lyophilized powder for injection. The objective of conjugation of IFN alfa with PEG is to improve the delivery of the protein by significantly prolonging its plasma half-life, and thereby provide protracted activity of IFN alfa.

The term " interferon-alfa " as used herein means the family of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation and modulate immune response. Typical suitable interferon-alfas include, but are not limited to, recombinant interferon alfa-2b such as Intron-A interferon available from Schering Corporation, Kenilworth, N.J., recombinant interferon alfa-2a such as Roferon interferon available from Hoffmann-La Roche, Nutley, N.J., recombinant interferon alpha-2C such as Berofor alpha 2 interferon available from Boehringer

Ingelheim Pharmaceutical, Inc., Ridgefield, CT., interferon alpha-n1, a purified blend of natural alfa interferons such as Sumiferon available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from the Glaxo-Wellcome Ltd., London, Great Britain. or a consensus alpha interferon such as those described in U.S. Patent Nos. 4,897,471 and 4,695,623 (especially Examples 7, 8 or 9 thereof) and the specific product available from Amgen, Inc., Newbury Park, CA, or interferon alfa-n3 a mixture of natural alfa interferons made by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, CT., under the Alferon Tradename. The use of interferon alfa-2a or alpha 2b is preferred. Since interferon alpha 2b, among all interferons, has the broadest approval throughout the world for treating chronic hepatitis C infection, it is most preferred. The manufacture of interferon alpha 2b is described in U.S. Patent No. 4,530,901.

Other interferon alfa conjugates can be prepared by coupling an interferon alfa to a water-soluble polymer. A non-limiting list of such polymers include other polyalkylene oxide homopolymers such as polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxide-based polymers, effectively non-antigenic materials such as dextran, polyvinylpyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Such interferon alfa-polymer conjugates are described in U.S. Patent No. 4,766,106, U.S. Patent No. 4,917,888, European Patent Application No. 0 236 987, European Patent Application No. 0510 356 0 593 868 and 0 809 996 (pegylated interferon alfa-2a) and International Publication No. WO 95/13090.

Pharmaceutical composition of pegylated interferon alfa-suitable for parenteral administration may be formulated with a suitable buffer, e.g., Tris-HCl, acetate or phosphate such as dibasic sodium phosphate/monobasic sodium phosphate buffer, and pharmaceutically acceptable excipients (e.g., sucrose); carriers (e.g. human serum

albumin), toxicity agents (e.g. NaCl), preservatives (e.g. thimerosol, cresol or benylalcohol), and surfactants(e.g. tween or polysorabates) in sterile water for injection. The pegylated interferon alfa-may be stored as lyophilized powders under a refrigeration at 2°-8°C. The reconstituted aqueous solutions are stable when stored between 2° and 8°C and used within 24 hours of reconstitution. See for example U.S. Patent Nos, 4,492,537; 5,762,923 and 5,766,582.

The term "patients having chronic hepatitis C infections" as used herein means any patient having chronic hepatitis C and includes treatment naive patients, relapsers and non-responders.

These patients having chronic hepatitis C include those who are infected with mutiple HCV genotypes including type 1 as well as those infected with,*inter alia*, HCV genotypes 2 2 and/or 3 as well as HCV genotypes 2, 3, 4, 5 and/or 6 and other possible HCV genotypes.

The term "treatment naive patients" as used herein means patients with chronic hepatitis C who have never been treated with ribavirin or any interferon, including but not limited to Interferon-alfa, or pegylated interferon alfa.

The term "relapsers" as used herein means patients with chronic hepatitis C who have relapsed after initial response to previous treatment with interferon alone, or in combination with ribavirin.

The term "non-responders" as used herein means patients with chronic hepatitis C who have not responded to prior treatment with any interferon alone, or in combination with ribavirin.

A person suffering from chronic hepatitis C infection may exhibit one or more of the following signs or symptoms:

(a) elevated ALT,

(b) positive test for anti-HCV antibodies,

(c) presence of HCV as demonstrated by a positive test for the presence of HCV-RNA in the serum,

(d) clinical stigmata of chronic liver disease,

(e) hepatocelluar damage.

To practice the invention, the combination therapy of pegylated interferon-alfa and ribavirin is administered to the patient exhibiting one of more of the above signs or symptoms in the first and second treatment time periods in amounts sufficient to eliminate or at least alleviate one or more of the signs or symptoms.

Ribavirin is administered to the patient in association with pegylated interferon-alfa, that is, the pegylated interferon-alfa dose is administered during the same period of time that the patient receives doses of ribavirin. Pegylated interferon-alfa formulations are not effective when administered orally, so the preferred method of administering the pegylated interferon-alfa is parenterally, preferably by subcutaneous, IV, or IM, injection. Ribavirin may be administered orally in capsule or tablet form in association with the parenteral administration of pegylated interferon-alfa . Of course, other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, by suppository, by sustained release dosage form, and by pulmonary inhalation. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient.

The term "no detectable HCV-RNA" in the context of the present invention means that there are fewer than 100 copies of HCV-RNA per ml

of serum of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HCV-RNA is preferably measured in the present invention by the methodology described below. This methodology is referred to herein as HCV-RNA/qPCR. The lower limit of detection of HCV-RNA is100 copies/mL

RNA is extracted from patient serum using a guaninidium thiocyanate- phenol-chloroform mister followed by ethanol-ammonium acetate precipitation. The precipitated RNA is centrifuged and the resulting pellet is dried in a Centrivap console (Labconco, Kansas City, Mo.). The dry pellet is then resuspended in 30 microliters of an Rnasin (Promega Corp., Madison, WI), dithiothritol, and diethylpyrocarbonate-treated water mixture. Samples are kept at or below -20°C (preferably below -70°C) until RNA reverse transcription (RT) and PCR.

In order to convert the entire RNA sequence into cDNA in the RT reaction, random hexadeoxyribonucleotides (Pharmacia Biotech, Piscataway, NJ) are used as primers for the first strand cDNA synthesis. Two aliquots of 3 microliters of resuspended sample are added to 3 microliters of 100ng/μl random primers and denaturated at 70°C, then reverse transcribed at 40°C for one hour using M-MLV reverse transcriptase (USB, Cleveland, OH) in standard buffer containing 5 mM $MgCl_2$. The final RT reaction volume is 26 μl. The PCR is started immediately following the reverse transcription.

A modified version of the PCR method is performed using heat-stable Taq polymerase to amplify the cDNA. Seventy-five microliters of PCR mix is added to the entire RT reaction volume (26 μl) to a final $MgCl_2$ concentration of 1.5 mM in a total volume of 101 μl. Each 101 μl sample is then split into 50.5 μl, and a layer of mineral oil is placed on top to prevent evaporation.

The PCR cycle consists of annealing for 90 sec., extension for 90 sec., and denaturation for 90 sec., at 55°C, 74°C and 94°C, respectively. Thermocycling samples is submitted to a final 74°C extension for 10 minutes. Four different cycle sets are used. By loading the sample in duplicate, and splitting these samples evenly after RT, there are four tubes from one sample. Each of the four tubes is given a different cycle number, enhancing sensitivity and accuracy in the quantitation process. The thermocycling efficiency will be assessed by satisfactory amplification of known copy number RNA standards included in each set of 60 tubes. Two primer sets are used for the amplification, both from the 5' untranslated region of the HCV genome. Both of these primer sets are highly conserved and detect all known subtypes of HCV. Primer set 1: upstream 5' -GTG GTC TGC GGA ACC GGT GAG T-3', downstream 5'-TGC ACG GTC TAC GAG ACC TC-3' which produces a 190 bp product. Primer set 2: upstream 5'-CTG TGA GGA ACT ACT GTC TTC-3', downstream 5'-CCC TAT CAG GCA GTA CCA CAA-3' which produces a 256 bp product.

The amplified cDNA is then electrophorised in 3% agarose gel and transferred to nylon membrane. The target DNA is detected by Southern blotting and immunostaining using a nonradioactive digoxigenin-labeled DNA probe. These procedures are performed using automated instruments for PCR thermocycling, agarose gel electrophoresis, vacuum-transfer Southern blot, hybridization, and immunostaining. Each membrane contains known copy number serially diluted standards which are used to construct standard curves for quantitative measurement of the specimen bands. Originally standard curves are made from carefully diluted HCV-RNA from transcribed clones. Radioactive incorporation studies, gel electrophoresis, and OD 260 are performed on the transcripts to determine that they are of the expected length. After the production of the RNA transcripts quantitated clone standards "pooled" standards are generated which better represent the heterogeneous nature of HCV, one would encounter in natural infection. These pools are made by combining

large amounts of serum or plasma from known infected individuals. The serum/plasma pools are calibrated with PCR, against the clone transcripts and then diluted in the known PCR-negative fluids. Finally, the higher copy number samples of the pools are checked against the cDNA Quantiplex nucleic acid detection system from Chiron Inc. (Emeryville, CA). These "double quantitated" pools are aliquoted and saved at -70°C. Dilutions of 5,000,000, 1,000,000, 500,000, 100,000, 10,000, and 1000 copies/ml are used in each experiment.

Each Southern blot membrane is scanned into a computer using an automated scanner/densitometer, at intervals during development to determine when the standard curve is most linear. The resultant electronic images are then measured for band area and mean band density. All of the reading are standardized to integrated band density and compared to the standard curve to obtain a numerical value of viral copy number for each band.

The term "sustained virologic response" as used in the context of the present invention means that there is no detectable HCV-RNA in the patients treated in accordance with the present invention for at least 24 weeks after the end of the combined therapy treatment. Preferably, the period of sustained virologic response will be at least one year - or longer - after the end of treatment. For HCV genotyping, INNO-L PA HCV (Innogenetics, Zeijmaurde, Belgium) second generation assay may be used.

The following clinical protocol may be used to administer the combination therapy of the present invention:

Overall Design and Plan of the Study

A prospective, multicenter, randomized, double-blind, parallel-group will be used. Two studies each with two treatment regimes will be used. Study No. 1 will compare treatment with pegylated Intron A, 1.5

micrograms per kilogram SC once a week (QW) in combination with ribavirin, 1000 to 1200 mg per day PO for four weeks followed by pegylated Intron A, 0.5 micrograms per kilogram SC once a week, in combination with ribavirin, 1000 to 1200 mg per day PO for forty-four weeks to treatment with pegylated Intron A, 1.5 micrograms per kilogram SC once a week in combination with ribavirin, 1000 to 1200 mg per day PO for forty-eight weeks. Study No. 2 will compare treatment of pegylated Intron A, 1.5 micrograms per kilogram SC BIW in combination with ribavirin, 1000-1200 mg/day PO for four weeks followed by pegylated INTRON A 1.5 micrograms/kilogram SC QW in combination with ribavirin, 1000-1200 mg/day PO for forty-four weeks to the treatment REBETRON Combination Therapy (Intron A, 3 MIU SC TIW in combination with ribavirin, 1000 to 1200 mg per day PO) for forty-eight weeks in patients with compensated chronic hepatitis C. Eligible patients are those 18-65 years of age, male and female subjects who should have chronic hepatitis C confirmed by positive serum HCV-RNA, liver biopsy, and laboratory tests.

Treatment group assignments should be made by a Central Randomization Center. The randomization procedure should be designed to attempt to balance the treatment groups, within and across sites, with respect to presence or absence of cirrhosis in the pretreatment liver biopsy, serum HCV-RNA/qPCR level, and HCV genotype.

During treatment and posttreatment follow-up, biochemical (ALT), virological (HCV-RNA), and histological (liver biopsy) examinations would be used to assess the nature and duration of response to study treatment. The primary efficacy variable will be the overall response defined as loss of serum HCV-RNA/qPCR (<100 copies/mL) as measured at 24 weeks following the end of therapy. In addition, a decrease in hepatic inflammation, an improvement in posttreatment liver biopsy as measured by the Knodell Histology Activity index (HAI) and normalization of ALT will also be examined as a secondary efficacy endpoints. The safety of the study treatments will be assessed by monitoring selected laboratory parameters and by also recording and evaluating the occurrence of any adverse events.

Treatment Regimens

There are two studies , each with two treatment regimens :

STUDY # 1

1. (a)Pegylated INTRON® A 1.5 micrograms per kilogram SC once a week (QW) plus ribavirin 1000-1200 mg/Kg/day PO in two divided doses for 4 weeks; followed by

(b)Pegylated INTRON® A 0.5 micrograms per kilogram SC INTRON® A once a week (QW) plus ribavirin 1000-1200 mg/Kg/day PO in two divided doses for 44 weeks.

2. (a) Pegylated INTRON® A 1.5 micrograms per kilogram once a week (QW) plus ribavirin 1000-1200 mg/Kg/day PO in two divided doses for 44 weeks.

STUDY # 2

3 (a) Pegylated INTRON® A 1.5 micrograms per kilogram twice a week (BIW) plus ribavirin 1000-1200 mg/Kg/day PO in two divided doses for 4 weeks; followed by

(b)Pegylated INTRON® A 1.5 micrograms per kilogram INTRON® A once a week (QW) plus ribavirin 1000-1200 mg/Kg/day PO in two divided doses for 44 weeks.

4. (a) INTRON® A 3 MIU SC three times a week (TIW) plus ribavirin 1000-1200 mg/Kg/day PO in two divided doses for 48 weeks.

Studies No. 1 and 2 including treatments 1 and 2 and 3 and 4 should be administered for 48 weeks.

Exclusion Criteria: Patients having chronic hepatitis C who should be excluded from treatment in accordance with the present invention include, *inter alia*., women who are pregnant or nursing; those with suspected hypersensitivity to pegylated interferon alfa or ribavirin; those with normal ALT at screenin or entry visit, as well as those with any known pre existing condition(e.g. pre existing psychiatric condition especially severe depression or a history of severe psychiatric disorder) that in the

opinion of the attending clinician would interfere with the subject's participation in and completion of the protocol.

The randomization procedure may be designed to balance the groups with respect to the following Baseline characteristics:

- pretreatment liver histology (cirrhosis or no cirrhosis);
- serum HCV-RNA/qPCR status (HCV-RNA/qPCR ≤2,000,000 or HCV-RNA/qPCR >2,000,000 copies/mL); and
- HCV Genotype (1 or other). Patients with mixed genotypes (which include Type 1) will be classified as Type 1 for purposes of balancing.

Efficacy

The primary efficacy objective will be the sustained virologic response rate defined as loss of (detectable) serum HCV-RNA/qPCR measured at 24 weeks following the end of therapy to an undetectable level or to a level <100 copies/mL. The following secondary efficacy Endpoints will also be examined:

The secondary efficacy Endpoints:

- proportion of patients with normalization of ALT at 24 weeks of follow-up;
- proportion of patients with improvement in biopsy (Categories I + II +III combined scores);
- change from Baseline in the biopsy scores (Categories I + II + III combined scores);
- response rates at Endpoint of treatment based on HCV-RNA/qPCR;
- proportion of patients with normalization of ALT at Endpoint of treatment.

- response rates at 24 weeks of follow-up based on HCV-RNA/qPCR.

5

Virology: Entry Status and Change from Entry

Serum HCV-RNA/qPCR testing and genotype testing will be performed by a central laboratory. A positive HCV-RNA assay result will be required at Baseline; only patients positive for HCV-RNA will be eligible to participate. Repeat assays should be scheduled at Weeks 4, 12, 24, 36 and 48. All patients should have repeat assays scheduled for Follow-up Weeks 12 and 24.

Response will be assessed as defined below:

A patient will be classified as a sustained responder at a given time point if HCV-RNA/qPCR is negative (<100 copies per mL) at that time point.

A patient will be classified as a sustained responder if the patient is a responder at 24 weeks of follow-up.

Note that patients who do not meet these criteria, including patients who discontinued before the required HCV-RNA/qPCR evaluations are obtained, will be classified as non-responders.

Based on both serum HCV-RNA/qPCR and change in liver histology as evaluated by the Knodell HAI Inflammation Score. A patient will be classified as an overall responder to treatment if he/she is a sustained responder and his/her Post treatment Knodell HAI inflammation score (sum of categories I+II+III) improved by 2 or more units relative to the Pretreatment score.

Liver Histology

Liver biopsy will be required within the six months preceding patient enrollment and at Follow-up Week 24 for all patients. Evaluation of the biopsies will be performed by a single pathologist using the Knodell Histology Activity Score. The central pathologist will be blinded with respect to patient identification, treatment group, and the time the biopsy will be obtained relative to treatment (Pre- or Posttreatment). Efficacy of study treatments will be assessed by comparing the degree of inflammatory activity observed at Baseline with that present at Follow-up Week 24.

The patient's weight and their baseline disease characteristics (HCV genotype and initial viral load) for all patients will be measured before the start of the study. HCV genotypes should be done on the patient serum samples subjected to HCV-RNA/qPCR testing.

This enhancement of efficacy included all aspects of the disease will result in:

- Sustained eradication of detectable HCV-RNA;
- Improvement in hepatic inflammation;
- Normalization of ALT;
- Improvement in HQL.

Claims

We claim:

1. The use of ribavirin for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods:(a) a first treatment time period, wherein a therapeutically effective amount of ribavirin and an therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to sustantially lower detectable HCV-RNA serum levels, and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to eradicate detectable HCV-RNA at least 20 to 30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

2. The use of pegylated interferon alpha for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of pegylated interferon alpha in association with an effective amount of ribavirin characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period,wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to sustantially lower detectable HCV-RNA serum levels, and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to eradicate detectable HCV-RNA at least 20 to 30

weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

3. The use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period, wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to sustantially lower detectable HCV-RNA serum levels, and by (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to eradicate detectable HCV-RNA at least 20 to 30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

4. The use of ribavirin for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period, wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to eradicate detectable HCV-RNA, and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of

ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to maintain no detectable HCV-RNA for at least 20-30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

5. The use of pegylated interferon alpha for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of pegylated interferon alpha in association with an effective amount of ribavirin characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period, wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to eradicate detectable HCV-RNA, and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to maintain no detectable HCV-RNA for at least 20-30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

6. The use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period, wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to eradicate detectable HCV-RNA, and (b) a second treatment time period of at least 20 to 30 weeks a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to maintain no detectable HCV-RNA for at least 20-30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

7. The use of any preceding claim, wherein the amount of ribavirin administered in the first and second treatment time periods is from 400 to 1600 mg per day, and preferably is from 600 to 1600 mg per day, or is 800 to 1200 mg per day, and more preferably is from 1000 to 1200 mg per day.

8. The use of any preceding claim, wherein the pegylated interferon-alfa administered is pegylated interferon alfa-2a,or pegylated interferon alfa-2b.

9. The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period is in the range of 0.5 to 1.5 micrograms per kilogram BIW for at least four weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period is in the range of 0.5 to 1.5 micrograms per kilogram per week on a weekly basis for up to forty-four weeks.

10. The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period is in the range of 0.5 to 1.5 microgram per /kilogram BIW for four to twelve weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period is in the range of 0.5 to 1.5 micrograms per kilogram per week on a weekly basis for thirty-six to forty-four weeks.

11. The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period of five weeks is in the range of 0.5 to1.5 micrograms per kilogram BIW for one week, followed by 0.5 to 1.0 micrograms per kilogram BIW for four weeks, and the amount of

pegylated interferon alfa-2b administered in the second treatment time period of forty-three weeks is in the range of 0.5 to 1.5 micrograms per kilogram per week on a weekly basis.

12. The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein, the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period is in the range of 0.5 to 1.5 micrograms/kilogram BIW for twelve weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period is in the range of 0.5 to 1.5 micrograms/kilogram per week on a weekly basis for thirty six weeks.

13. The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period of five weeks is in the range of 0.5 to 1.5 micrograms/kilogram BIW for one week, followed by 1.0 micrograms/kilogram BIW for four weeks and the amount of pegylated interferon alfa-2b administered in the second treatment time period of forty-three weeks is in the range of 0.5 to 1.0 micrograms/kilogram per week on a weekly basis.

14. The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period is 1.5 micrograms/kilogram BIW for twelve weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period is 1.5 micrograms/kilogram per week on a weekly basis for thirty- six weeks.

15. The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of

pegylated interferon alfa-2a administered is from induction dosing amount of pegylated interferon alfa-2a administered is in the range of 20 to 250 micrograms BIW, preferably 90 to 180 micrograms BIW, for at least four weeks, and the amount of pegylated interferon alfa-2a administered in the second treatment time period is in the range of 20 to 250 micrograms per week on a weekly basis(QW), 90 to 180 micrograms QW, for up to forty four weeks.

16. The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and wherein in first treatment time period, the induction dosing amount of pegylated interferon alfa-2a administered is in the range of 20 to 250 micrograms BIW , preferably 90 to 180 micrograms BIW, for four to twelve weeks, and the amount of pegylated interferon alfa-2a administered in the second treatment time period is in the range of 20 to 250 micrograms per week on a weekly basis(QW), preferably 90 to 180 micrograms QW, for thirty six to forty four weeks.

17. The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and wherein in first treatment time period, the induction dosing amount of pegylated interferon alfa-2a administered is in the range of 20 to 250 micrograms BIW for one week, preferably 90 to 180 micrograms BIW, for one week, followed by 20 to 200 micrograms BIW, preferably 120 to 180 micrograms BIW, for four weeks, and the amount of pegylated interferon alfa-2a administered in the second treatment time period administered is in the range of 20 to 250 micrograms per week on a weekly basis(QW), preferably 90 to 180 micrograms QW, for forty-three weeks.

18. The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated Interferon alfa-2a and wherein in first treatment time period, the induction dosing amount of pegylated interferon alfa-2a administered is in the range of 20 to 250 micrograms

BIW, preferably 90 to 180 micrograms BIW,for twelve weeks, and the amount of pegylated interferon alfa-2a administered in the second treatment time period is in the range of 20 to 250 micrograms per week on a weekly basis(QW), preferably 90 to 180 micrograms QW, for thirty-six weeks.

19. The use of any preceding claim wherein the patients having chronic hepatitis C are infected with multiple HCV genotypes including type 1.

20. The use of any preceding claim wherein the patients having chronic hepatitis C are infected with HCV genotype 2 and/or 3.

21. The use of any preceding claim wherein the patient is a treatment naïve patient.

22. The use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (1) a first treatment time period of about at least about four weeks, wherein about 400-1200 mg per day, preferably about 800-1200 mg per day, of ribavirin and about 1.5 micrograms per kilogram of pegylated interferon-alfa-2b twice a week are administered, (2) a second treatment time period of about up to about forty-four weeks, wherein about 800-1200 mg per day of ribavirin and about 1.0 to 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week are administered.

23. The use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a

method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (1) a first treatment time period of about at least about four up to about twelve weeks, wherein about 400-1200 mg per day, preferably about 800-1200 mg per day, of ribavirin and about 1.5 micrograms per kilogram of pegylated interferon-alfa-2b twice a week are administered, (2) a second treatment time period of about thirty-six up to about forty-four weeks, wherein about 800-1200 mg per day of ribavirin and about 0.5 to 1.5 micrograms per kilogram, preferably about 1.0 to 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week are administered.

24. The use of claims 22 or 23, wherein the patients having chronic hepatitis C infection are treatment naive patients having HCV genotype 1, 2 or 3.

25. The use of claims 22 or 23,, wherein the induction dosing amount of pegylated interferon alfa-2b administered in secondt time period is 1.5 micrograms/kilogram

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: **A61K 38/21, A61K 31/7056, A61P 31/14**	**A3**	(11) International Publication Number:	**WO 00/37110**
		(43) International Publication Date:	29 June 2000 (29.06.2000)

(21) International Application Number: PCT/US99/27935

(22) International Filing Date: 16 December1999 (16.12.1999)

(30) Priority Data:
09/215,876 18 December1998 (18.12.1998) US

(60) Parent Application or Grant
SCHERING CORPORATION [/]; (). GLUE, Paul, W. [/]; (). ALBRECHT, Janice, K. [/]; (). HOFFMAN, Thomas, D. ; ().

Published

(54) Title: RIBAVIRIN-PEGYLATED INTERFERON ALFA INDUCTION HCV COMBINATION THERAPY
(54) Titre: TRAITEMENT DU VHC PAR INDUCTION D'INTERFERON-ALPHA PEGYLE COMBINE LA RIBAVIRINE

(57) Abstract

The use of ribavirin and interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatitis C infection, e.g., a patient having HCV genotype 1, 2 or 3, to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period of at least 20 to 30 wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa, e.g., pegylated interferon-alfa-2b sufficient to at least substantially lower, and preferably to eradicate, detectable HCV-RNA, are administered; and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to maintian no detectable HCV-RNA for at least 20-30 weeks are administered after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period is disclosed.

(57) Abrégé

L'invention concerne l'utilisation de ribavirine et d'interféron alpha pour la préparation de compositions pharmaceutiques dans le traitement d'un patient souffrant d'hépatite C chronique, notamment un patient dont le génotype du VHC est 1, 2 ou 3. Cette utilisation vise à éradiquer le taux de l'ARN du VHC détectable en mettant un oeuvre un procédé consistant à administrer une quantité efficace de ribavirne associée à une quantité efficace d'interféron alpha pégylé. Le traitement du patient souffrant d'hépatite C chronique s'effectue en deux temps : a) une première période d'au moins 20 à 30 semaines au cours de laquelle on administre une quantité thérapeutiquement efficace de ribavirine et une quantité inductive thérapeutiquement efficace d'interféron alpha pégylé, à savoir l'interféron alpha pégylé 2b en doses suffisantes pour diminuer considérablement et supprimer, dans la mesure du possible, le taux de l'ARN du VHC détectable; et b) une seconde période de traitement s'étendant sur 20 à 30 semaines au cours de laquelle on administre une quantité thérapeutiquement efficace de ribavirine et une quantité thérapeutique efficace d'interféron alpha pégylé en quantités suffisantes pour que le taux de l'ARN du VHC ne soit pas détectable pendant au moins 20 à 30 semaines après la fin de la période du premier traitement et en quantités suffisantes pour que le taux de l'ARN VHC ne soit pas détectable pendant au moins 24 semaines une fois que le second traitement est terminé.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 38/21, 31/7056, A61P 31/14 — A3

(11) International Publication Number: WO 00/37110

(43) International Publication Date: 29 June 2000 (29.06.00)

(21) International Application Number: PCT/US99/27935

(22) International Filing Date: 16 December 1999 (16.12.99)

(30) Priority Data:
09/215,876 18 December 1998 (18.12.98) US

(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).

(72) Inventors: GLUE, Paul, W.; 13 Allens Corner Road, Flemington, NJ 08822 (US). ALBRECHT, Janice, K.; 1308 Temple Grove Court, Winter Park, FL 32789 (US).

(74) Agents: HOFFMAN, Thomas, D. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(88) Date of publication of the international search report:
14 September 2000 (14.09.00)

(54) Title: RIBAVIRIN-PEGYLATED INTERFERON ALFA INDUCTION HCV COMBINATION THERAPY

(57) Abstract

The use of ribavirin and interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatitis C infection, e.g., a patient having HCV genotype 1, 2 or 3, to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period of at least 20 to 30 wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa, e.g., pegylated interferon-alfa-2b sufficient to at least substantially lower, and preferably to eradicate, detectable HCV-RNA, are administered; and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to maintian no detectable HCV-RNA for at least 20-30 weeks are administered after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period is disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/27935

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/21 A61K31/7056 A61P31/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	P. GLUE ET AL.: "A DOSE-RANGING STUDY OF PEG-INTRON AND RIBAVIRIN IN CHRONIC HEPATITIS C. SAFETY, EFFICACY AND VIROLOGIC RATIONALE" HEPATOLOGY (SUPPLEMENT), vol. 30, no. 4(2), October 1999 (1999-10), page 303A XP002138613 USA abstract -/--	1-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2000	28/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Economou, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inta onal Application No
PCT/US 99/27935

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	M.SULKOWSKI ET AL.: "COMBINATION THERAPY WITH PEGINTERFERON ALPHA-2A (PEG-IFN) AND RIBAVIRIN IN THE TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS C (CHC)" HEPATOLOGY (SUPPLEMENT), vol. 30, no. 4(2), October 1999 (1999-10), page 197A XP002138614 USA abstract	1-25
P,X	JAYANT TALWALKAR ET AL.: "COMBINATION THERAPY WITH INTERFERON-ALFA-2B (INTRON-A) AND RIBAVIRIN (REBETOL) IN CHRONIC HEPATITIS C PATIENTS PREVIOUSLY RELAPSING OR NOT RESPONSING TO INTERFERON" HEPATOLOGY (SUPPLEMENT), vol. 30 , no. 4(2), October 1999 (1999-10), page 197A XP002138615 USA abstract	1-25
P,X	ALGRANATI N.E. ET AL.: "A BRANCHED METHOXY 40 KDA POLYETHYLENE GLYCOL (PEG) MOIETY OPTIMIZES THE PHARMACOKINETICS (PK) OF PEGINTERFERON ALPHA-2A (PEG-IFN) AND MAY XPLAIN ITS ENHANCED EFFICACY IN CHRONIC HEPATITIS" HEPATOLOGY (SUPPLEMENT), vol. 30, no. 4(2), October 1999 (1999-10), page 190A XP002138616 USA abstract	1-25
P,X	MITCHELL SCHIFFMAN MITCHELL ET AL.: "CONTROLLE, RANDOMIZED, MULTICENTER, DESCENDING DOSE PHASE II TRIAL OF PEGYLATED INTERFERON ALPHA-2A (PEG) VS STANDARD INTERFERON ALPHA-2A (IFN)FOR TREATMENT OF CHRONIC HEPATITIS C" GASTROENTEROLOGY, vol. 116, no. 4(2), April 1999 (1999-04), page 1275 XP002138617 USA abstract	1-25
P,X	EP 0 956 861 A (SCHERING CORPORATION) 17 November 1999 (1999-11-17) the whole document claims 1-12	1-25
P,X	EP 0 903 148 A (SCHERING CORPORATION) 24 March 1999 (1999-03-24) the whole document claims 1-18	1-25

-/--

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)